REMARKS

Claims 1- 30 are pending in the instant application. Claims 18-29 have been withdrawn from consideration. Claims 1-17 and 30 have been rejected.

Claims 1, 9 and 16 have been amended.

The Amendments

As directed by the Examiner, the specification has been amended to claim priority to provisional applications 60/079,956 filed December 16, 1998 under 35 U.S.C. § 119(e).

Claim 1 has been amended to correct the spelling of "spacially" to "spatially."

Claim 9 has been amended to spell out the abbreviated claim terminology "TR," "RAR," "RXR," "PPAR," "VDR," "ER," "GR," "PR," "MR," and "AR."

Claim 16 has been amended to spell out the abbreviated terminology "NR-box" and to add the word "test" before "compound."

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-17, and 30 have been rejected under § 112, first paragraph, as not enabling for identifying compounds by any other method than the activation of transcription by binding hTR-beta and hER-alpha. The Examiner asserts that the specification "offers no other method for identifying if a test compound modulates coactivator binding to a nuclear receptor other than through testing the effects of binding on transcription." The Examiner cites Example 9.

As the Examiner is aware, enablement does not require working examples. *See* MPEP § 2164.02. The presence of one working example is sufficient for enablement. The specification need not even contain a working example if the claimed invention is otherwise disclosed in a manner that one skilled in the art is able to practice the invention without undue experimentation. *Id.*

Claim 1 recites the screening of test compounds in an assay characterized by binding of a test compound to a nuclear receptor coactivator binding site, and identifying a test compound that modulates coactivator binding to said nuclear receptor. In claim 1 and dependent claims 2-16, compounds that modulate coactivator binding are identified by assays characterized by **binding of a test compound to the coactivator site**. The binding of a test compound that is modeled in the coactivator binding site will modulate (affect in some way) coactivator binding to a nuclear receptor. The binding assays disclosed in the specification at pages 15-16 are sufficient to identify which compounds modulate coactivator binding and thus to enable these claims.

Claim 17, the other independent claim, recites identifying in an assay for nuclear receptor activity a compound that increases or decreases the activity of said nuclear receptor by binding the coactivator binding site of said nuclear receptor.

At page 4, lines 13-18, the specification discloses that a method of modulating the activity of a nuclear receptor is provided, comprising administering, *in vitro* or *in vivo*, a sufficient amount of a compound that binds to the coactivator binding site. The bound compound can compete for binding of coactivator proteins, thereby inhibiting gene transcription or promoting it. One does not, however, need to test for the effect on transcription to determine whether the compound is competing for binding.

The specification further provides at page 15, line 28 to page 16, line 22 that the claimed assays may be biological assays. Further, that preferred assays include cell-free competition assays **and** cell culture based assays. The biological screening preferably centers on activity-based response models, binding assays (which measure how well a compound binds to the receptor), and bacterial, yeast and animal cell lines (which measure the biological effect of a compound in a cell.) In vitro binding assays can be performed in which compounds are tested for their ability to block the binding of a coactivator protein, fragment etc. to a coactivator binding site of interest. For cell and tissue culture assays, they may be performed to assess a compound's ability to block function of cellular coactivators, such as members of the p160 family of coactivator proteins, and those that exhibit receptor and/or isoform-specific binding affinity. In a preferred embodiment, compounds bind to a coactivator binding site with greater affinity than the cellular coactivator proteins. Tissue profiling and appropriate animal models

also can be used to select compounds. Different cell types and tissues also can be used for these biological screening assays. Numerous suitable screening assays are described in the prior art and are cited in the specification.

Finally, the specification discloses, at page 16, lines 23-32, that the agonist or antagonist properties of the compounds can modulate nuclear receptor activity that is hormone dependent or independent, and modulated by proteins other than coactivators and which interact with receptors at locations other than the coactivator binding site. The compounds may have allosteric effects on the receptor by stabilizing or destabilizing the hormone-bound configuration of the receptor, or by directly inducing the same or different conformational changes induced in the receptor by binding of the hormone. Thus, the specification discloses ways to determine whether a compound modulates coactivator binding other than through testing the effects of binding on transcription.

Claims 1-17 and 30 also are rejected under § 112, first paragraph, as not enabled for nuclear receptors not containing cofactor binding sites. By "cofactor binding sites," applicant assumes the Examiner means "coactivator binding sites."

The Examiner asserts that it is not clear that the broad group of nuclear receptors necessarily have coactivator binding sites. The specification, however, clearly discloses at page 2, lines 6-7, that sequence conservation between functional regions of the receptors is high, including the ligand binding domain ("LBD"). The specification further discloses at page 9, and Figure 19, that the coactivator binding site is **highly conserved** among the nuclear receptor superfamily. In addition, the hydrophobic cleft of the coactivator binding site also is highly conserved. Thus, one of skill in the art would expect to find the coactivator binding site in most, if not all, nuclear receptors.

Secondly, the Examiner's assertion that it would require undue experimentation to identify compounds that modulate cofactor binding with undisclosed nuclear receptors because it is uncertain if they contain a coactivator binding site is unfounded. A considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.05(b), *citing In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The specification gives sufficient guidance, first by

pointing out how to identify coactivator binding sites by **homology** to the coactivator binding site of human TR. The specification further discloses at pages 9-10, a preferred method for identifying such sites, namely, alignment with specified residues of any nuclear receptor ("NR") corresponding to human TR residues of C-terminal helices 3, 4, 5, 6, and 12. The specification indicates that overlays and superpositioning with a three dimensional model of a NR LBD that contains a coactivator binding site can be used for this purpose. At page 10, lines 8-13, the specification specifically discloses that the nuclear receptors identifiable by homology alignment include normal nuclear receptors or proteins structurally related to nuclear receptors found in humans, natural mutants of nuclear receptors found in humans, normal or mutant receptors found in animals, as well as non-mammalian organisms such as pests or infectious organisms or viruses.

Thus the specification discloses that coactivator binding sites are to be expected in most if not all nuclear receptors. Secondly, the specification provides detailed disclosure of how to identify such compounds by computational modeling and/or screening. The specification provides sufficient guidance such that any experimentation required to identify such compounds would not be undue.

For these reasons, applicant respectfully requests that the Examiner withdraw the § 112, first paragraph rejections.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 1-17 and 30 are rejected under § 112, second paragraph, as being indefinite. As suggested by the Examiner, Claim 9 has been amended to spell out abbreviated terminology. The Examiner has indicated that claim 9 also is indefinite because of the term "NR-box." Claim 9, however, does not contain the term "NR-box." Claim 16, which does contain the term, has been amended to spell out the abbreviation. The term "NR-box" is well known in the art, as indicated by its reference in prior art literature cited in this application.

The Examiner has rejected claim 1 under § 112 because "applicant appears to be screening compounds using a competition assay, but is not clearly stating this." The specification discloses, at page 15, line 28 to page 16, line 22, that the recited assay is not

limited to a competition assay. Thus, while the Examiner has not clearly stated the basis of the rejection, the specification provides support for screening compounds with different types of assays.

With respect to claim 12, the Examiner has stated the term "biological activity" is unclear. The term that appears in claim 12 is "biological **assay**," not "biological **activity**." The term "biological assay" is clearly defined at pages 15-16 of the specification, and thus the applicant submits that the term is not unclear.

With respect to claim 11, the Examiner asserts that the term "high throughput screening" is vague and indefinite because "high" is comparative terminology and does not designate unique or distinct value. The term "high throughput screening" denotes a type of automated screening that is well known and understood to those of ordinary skill in the art. See specification at page 15, lines 34-36. Applicant submits that it is not a vague or indefinite term.

With respect to claims 2-8, the Examiner has stated that the terms "corresponding to residues of human thyroid receptor" are indefinite. The term "corresponding to" is defined in the specification at page 9, line 34 as "equivalent to." Accordingly, the term is not indefinite.

For the reasons discussed above, applicant respectfully requests that the rejections under § 112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 102(a) Over Darimont

The Examiner has rejected claims 1-10, 12, 14-17, and 30 under § 102(a) over Darimont et al. The Darimont reference, which has a publication date of November 1, 1998, can be considered a prior art reference only if the Examiner considers the priority date of this application to be the filing date of the provisional application 60/113,146, December 16, 1998. If the priority date is March 30, 1998, because of the claim to priority under § 119(e) to provisional application 60/079,956, Darimont can no longer serve as a prior art reference.

The specification has been amended to claim priority to this provisional application. The Examiner has indicated that the oath is defective because the last two

digits of the serial number of the provisional application were transposed, and that until the oath is corrected, the priority date for this application is the effective filing date of December 16, 1998. A revised declaration has been prepared which reflects the proper serial number, and it will be submitted to the Office as soon as the inventors have executed it. With the revised declaration, the priority date of March 30, 1998 is clearly established.

For these reasons, applicant respectfully requests that the § 102(a) rejection over Darimont be withdrawn.

Rejection Under 35 U.S.C. § 102(b) Over Scanlan

The Examiner has rejected claims 1, 5, 9-10, 12, 15, and 17 under § 102(b) over Scanlan et al. The Scanlan reference is a PCT application, WO 97/21993, with a publication date of June 19, 1997.

Section 2131 of the MPEP plainly states that to anticipate a claim, the reference must teach each and every element of the claim. The Federal Circuit's instruction on this point also is clear. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987). *See also, Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) (identical invention must be shown in as complete detail as set forth in claim). For a process claim, anticipation requires identity of the claimed process and a process of the prior art. *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550 (Fed. Cir. 1995). The claimed process, including each step thereof, must have been described or embodied, either expressly or inherently, in a single reference. *Id.* The elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831 (Fed. Cir. 1990).

The Examiner asserts that Scanlan discloses that "thyroid receptor ligands increase (i.e., modulate or agonize) nuclear receptor coactivation such that the binding of the coactivator protein, RIP-140, is enhanced upon binding of the ligand." Scanlan

teaches methods for the generation of nuclear receptor synthetic ligands based on the three dimensional structure of nuclear receptors. In Example 3, after the ligand binds to the nuclear receptor, the coactivator protein is bound. This example illustrates a number of ligands, which increase nuclear protein coactivation.

According to Scanlan, ligand binding allows the activation domain to serve as an interaction site for essential coactivator proteins that function to stimulate or inhibit transcription. See page 10, lines 6-0. The C-terminal activation subdomain is in close three dimensional proximity in the LBD to the ligand, to allow ligands bound to the LBD to coordinate (or interact) with amino acids in the activation subdomain. See page 10, lines 10-13. Scanlan further discloses that coactivation proteins interact with the nuclear receptors in a ligand-dependent way and that binding of these proteins can be modulated using the TR ligands described. See page 21, lines 14-15.

Scanlan does **not** disclose the binding of the ligand to the coactivator binding site. The ligand instead binds to the LBD in the **ligand binding cavity**. Thus, although the Examiner may be correct that the disclosed ligands modulate the binding of coactivator proteins, they do not do so by **binding to the coactivator site** as required by the claims.

Scanlan discloses that the nuclear receptor ligand is bound in a water inaccessible binding cavity in the LBD, and that chemical moieties can be added to selected positions on the ligand to make for a tighter fit or to disrupt or make contact with amino acids not in contact with the ligand before chemical modification. See page 22, lines 19-25. Scanlan further discloses that nuclear receptor LBDs usually have activation domains that present a region for binding to DNA and can be modulated by the binding of a ligand to the LBD. An extended chemical moiety from the ligand that disrupts binding or contact with the activation domain can be designed using computational methods. See page 26, lines 13-18. Such extended moieties will extend past and away from the molecular recognition domain on the ligand and past the buried binding cavity of the ligand in the direction of the activation domain. See page 26, lines 18-21.

Thus Scanlan does not teach that ligands are modeled in the coactivation binding site. Rather it clearly states that the ligands are modeled in the **ligand binding cavity** and that attached chemical moieties may extend toward the activation domain. In Scanlan, the test compounds are the TR ligands. These TR ligands are not modeled in

the coactivation binding site nor are they screened by an assay characterized by binding of the test compound to the coactivation binding site. The coactivator protein, RIP-140, is known, and is not a test compound. The ligand binds to the binding cavity, and then the known coactivator protein binds to the coactivator binding site. Scanlan tests the ability of the bound ligand to modulate the binding of the coactivator protein. This is **not** the claimed invention. Because Scanlan does not teach each element of the claimed invention, it cannot serve as an anticipatory reference.

For these reasons, applicant respectfully requests that the § 102(a) rejection over Scanlan be withdrawn.

Rejection Under 35 U.S.C. § 102(b) Over Glass

The Examiner has rejected claims 1, 5, 9-10, 12, 15, and 17 under § 102(b) over Glass et al. The Examiner asserts that Glass discloses a method of identifying a compound that modulates coactivator binding to a nuclear receptor. Glass does not teach a method that encompasses each and every element of the claimed method, as it must to serve as an anticipatory reference.

The Examiner asserts that Glass discloses the atomic model of the RXR-alpha ligand binding domain (Fig. 1) to model interaction of coactivator compounds such as SRC-1 and TIF2 (Fig. 3). Contrary to the Examiner's position, Glass does not teach the modeling step of the claim. As stated at page 222 of Glass, "crystal structures have not yet been solved for a **single** LBD in the liganded or unliganded states." What Glass discloses in Figure 1 is the crystal structure of the unliganded LBD of RXR-alpha and the crystal structure of the liganded RAR LBD. The authors make certain assumptions about the changes in structure of a LBD upon binding of the ligand based on these two crystal structures of different LBDs. Figure 1 does not show the binding of coactivator compounds to the coactivator binding site. Figure 1 does not even identify the coactivator binding site. Figure 1 certainly does not suggest modeling of coactivator compounds in the coactivator binding site, as explicitly taught and claimed in the instant application.

Figure 3 shows a possible mechanism (a "cartoon") for the roles of coactivator compounds in transcriptional activation by nuclear receptor dimers and heterodimers. Figure 3 does not show atomic models, and has no relationship to Figure 1. Thus, Glass does not teach or even suggest modeling of test compounds in the coactivator binding site. The Examiner has cobbled together two unrelated Figures to suggest a teaching of the modeling step where none exists and none was intended. In contrast, the specification of the instant application explicitly teaches at page 3, lines 24-29, and page 9, lines 13-15, that the modeling step uses an atomic structural model derived from co-crystals of the liganded and unliganded states of the LBD of the same nuclear receptor.

The Examiner asserts that Glass discloses biochemical assays for screening and identification, including expression cloning studies to identify potential coactivator compounds which modulate nuclear receptor function by affecting the transactivation domain. In Glass, the identification of nuclear receptor interacting proteins by expression cloning studies is not preceded by the modeling of test compounds that fit spatially into a nuclear receptor coactivator binding site using an atomic structural model. Rather, Glass used strategies based on genetic screens, yeast 2-hybrid systems and direct expression screening of bacteriophage cDNA libraries as a starting point to clone cDNAs encoding potential coactivator proteins, not to screen previously modeled test compounds. Contrary to the Examiner's suggestion, there is no relationship in Glass between the model shown in Figure 1 of the structure of the liganded and unliganded LBDs of different nuclear receptors and the biochemical assays to identify nuclear receptor interacting proteins by expression cloning studies that would teach the claimed method. Accordingly, Glass does not disclose the screening step of the claimed method.

For a process claim, anticipation requires identity of the claimed process and a process of the prior art. *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550 (Fed. Cir. 1995). The claimed process, including each step thereof, must have been described or embodied, either expressly or inherently, in a single reference. *Id.* The elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831 (Fed. Cir. 1990). Here, there is no identity of method disclosed in Glass with the claimed method. Glass does not disclose a method of identifying compounds that modulate coactivator binding to a nuclear receptor based on molecular modeling, but rather

discloses the identification of certain coactivator molecules based on expression cloning studies. Each step of the claimed method in the order recited in the claims is not disclosed in Glass. Although Glass disclosed a model of a liganded LBD, various biochemical assays, and the identification of some potential coactivator proteins through expression studies, these disclosures do not comprise a cohesive teaching of the claimed method. When Glass is viewed as a whole for what it teaches, it in no way discloses the claimed method of identifying compounds that modulate coactivator binding to a nuclear receptor.

For these reasons, applicant respectfully requests that the § 102(b) rejection over Glass be withdrawn.

Rejection Under 35 U.S.C. § 103 Over Darimont in View of Kuntz

As discussed above with respect to the § 102(a) rejection over Darimont, Darimont can only be a prior art reference if the Examiner looks to the filing date of the instant application. The effective filing date of this application actually is March 30, 1998, based on the claim of priority to provisional application 60/076,956. Therefore, Darimont cannot serve as a proper prior art reference once the typographical error in the oath is corrected to indicate the correct serial number of the provisional application to which priority is claimed.

As implicitly conceded by the Examiner in combining Kuntz with Darimont, Kuntz alone does not teach or suggest every element of the claimed invention. Thus, without Darimont, the rejection cannot be maintained.

For these reasons, applicant respectfully requests that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 103 Over Scanlan in View of Kuntz

The Examiner has rejected claims 1, 5, 9-13, 15, and 17 under § 103 over Scanlan in view of Kuntz et al. For the reasons discussed above, Scanlan does not anticipate or render obvious the claims because it does not disclose or suggest each and every element of the claims. Specifically, Scanlan fails to teach or suggest the modeling of test

compounds in the coactivator binding site. Furthermore, Scanlan does not teach screening by an assay characterized by binding of the test compound to the **coactivator binding site**. The test compounds in Scanlan are nuclear receptor ligands that bind in the **ligand binding cavity** and may have chemical moieties attached that extend toward the coactivation binding site. Because Scanlan fails to teach at least two limitations of the claims, it cannot possibly teach the claimed invention.

Kuntz does not supply the missing steps. The Kuntz reference is a discussion of drug design strategies, including the combination of structure determination and computational efforts. The article focuses on the computer program, DOCK, which the authors developed. DOCK is used to fit putative ligands into appropriate binding sites on receptors. Kuntz further discloses that a starting point is an x-ray crystallographic structure of the macromolecule. *See* page 1079. DOCK characterizes the entire surface of the receptor to characterize potential binding sites. *See* page 1080. The next step matches computer derived or x-ray structures of putative ligands to the image of the receptor based on a comparison of internal distances. The program then searches 3-D databases for small molecules that fit and evaluates them on the basis of the best orientations that can be found. Kuntz does not discuss the modeling of test compounds to coactivator sites of nuclear receptors and accordingly, does not remedy the deficiency of Scanlan.

Thus even if the references were combined, the combination would not render obvious the claimed invention.

For these reasons, applicant respectfully requests that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 103 Over Glass in View of Kuntz

The Examiner has rejected claims 1, 5, 9-13, 15 and 17 under § 103(a) over Glass et al. in view of Kuntz. For the reasons discussed above, Glass does not teach all of the elements of the claims. Specifically, Glass does not teach the step of modeling a test compound in the coactivator binding site. The Examiner has attempted to piece together this step of the claimed invention from two unrelated figures. Furthermore, Glass does not use biochemical assays to screen previously modeled test compounds, but rather as a

starting point to identify certain nuclear receptor interacting proteins with expression studies. Accordingly, Glass does not teach or suggest at least two limitations of the claims.

As discussed above, Kuntz, a generalized article about drug design which focuses on the computer program, DOCK, cannot teach or suggest the missing steps. Thus even in combination, the cited references do not render obvious the claimed invention.

For these reasons, applicant respectfully requests that the § 103 rejection over Glass in view of Kuntz be withdrawn.

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 843-5000.

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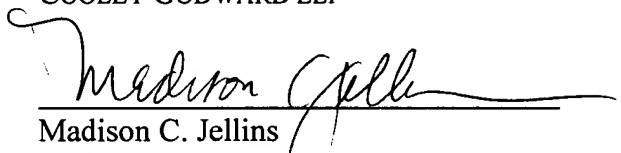
By: 
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